REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the amendments above and comments below.

Claims 1-45 are pending in the subject application. Claims 21, 22 and 26-46 have been withdrawn from consideration. Accordingly, claims 1-20, and 23-25 are presented for examination on the merits.

The language of claim 1 has been amended merely to make explicit that which was implicit in the original claim. Claims 2 and 3 have been amended to delete reference to genes associated with a tumor; claims 10 and 11 have been amended to delete reference to specific genes. Claim 18 has been amended to further define a genetically tractable organism.

No new matter is added by the amendments to the claims.

A copy of the Supplemental Information Disclosure Statement and Form 1449 filed June 25, 2002 are enclosed herein, together with the stamped post card which indicates that a Form 1449 had been filed. Accordingly, Applicant respectfully requests that the reference cited on the Form 1449 be considered by the Examiner.

I. Rejection of Claims 1-20 and 23-25 Under 35 U.S.C § 112, Second Paragraph

Claims 1-20 and 23-25 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is respectfully traversed as follows.

Claim 1 has been amended to more specifically define the secondary site mutation as one which results in a gene or protein that is non-functional. The claim has also been amended to clarify that the identity of the gene or protein effected by the secondary site mutation is determined in order to provide a secondary drug target. Thus, these amendments to claim 1 merely make explicit that which was implicit in the original claim language and do not substantively alter the claim.

Claims 2 and 3 have been amended to more particularly define the primary site mutation as one which is found in a human tumor cell.

Applicants acknowledge the finality of the restriction requirement and have elected p53 as the gene comprising a primary defect.

Claims 1-20 and 23-25 are rejected under 35 U.S.C § 112, second paragraph. The Examiner states that the claims are indefinite for failing to particularly point out and distinctly claim the subject which applicant regards as the invention.

It is respectfully submitted that the rejection of claim 1 is rendered moot by the amendment thereto.

It is respectfully submitted that he rejection of claim 2 is rendered moot by the amendment thereto.

The Examiner states that claims 3 and 12 are vague and indefinite in that the metes and bounds of the phrase "analogous or homologous to a defect found in . . ." because it is unclear what the degree of sequence identity or functional similarity is required.

This ground of rejection is respectfully traversed. The specification clearly defines the terms "analogous" and "homologous." At page 12 of the specification the terms "analogous" and "homologous" are defined as follows. "Two nucleic acid molecules are

determined to be homologous if their nucleic acid sequences share a similarity of greater than 40% as determined by HASH-coding algorithms" The specification also states that homologous genes have a direct relationship among a family of genes in which certain sequences or domains are strongly conserved among the family members. The specification also provides an example of homologs: the yeast mec1 gene and the mammalian genes encoding AT-related kinase. Thus, the specification provides the degree of sequence similarity and functional similarity

The term "analogous" is also defined at page 12 of the specification as referring to genes that are not related (do not have conserved sequences), but which have similar functions.

These definitions are also art recognized, as evidenced by the enclosed appropriate pages of Stedman's Medical Dictionary.

As such, the rejection of claim 3 and 12 under 35 U.S.C § 112, second paragraph is respectfully traversed.

The Examiner states that claims 10, 11, 14 and 24 are vague and indefinite because they specify that the secondary site is in a specified gene. This rejection is respectfully traversed.

Claims 10, 11, 14 and 24 specify that the secondary mutation is in a gene encoding a specified protein, but do not specify a particular gene encoding the protein. Thus, multi-allelic gene families, for example, are encompassed by this claim and specific alleles may serves as drug targets.

It is respectfully submitted that cancellation of claim 14 renders this ground of rejection moot.

Accordingly, the rejection of claims 1-20 and 23-25 under 35 U.S.C § 112, second paragraph is respectfully traversed.

It is respectfully submitted that the present application, as amended above, is in condition for allowance, an early notification thereof being earnestly solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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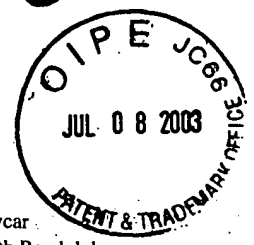

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...of the same or a closely related species. [homo- + G. ... + *tropē,* a turning toward]

ho·mo·dont (hō′mō-dont). Having teeth all alike in form, as in the lower vertebrates, in contrast to heterodont. [homo- + G. *odous,* tooth]

ho·mod·ro·mous (hō-mod′rō-mŭs). Moving in the same direction. [homo- + G. *dromos,* running]

homoeo-. SEE homeo-.

ho·mo·er·ot·ism; ho·mo·e·rot·i·cism (hō-mō-er′ō-tizm, -ĕ-rot′...). SYN homosexuality. [homo- + G. *erōs,* love]

ho·mo·ga·met·ic (hō′mō-gă-met′ik). Producing only one type of gamete with respect to sex chromosomes; in humans and most mammals the female is h. SYN monogametic. [homo- + G. *gametikos,* connubial]

ho·mog·a·my (hō-mog′ă-mē). Similarity of husband and wife in a specific trait. [homo- + G. *gamos,* marriage]

ho·mog·e·nate (hŏ-moj′ĕ-nāt). Tissue ground into a creamy consistency in which the cell structure is disintegrated (so-called "cell free"). Cf. brei.

ho·mo·ge·neous (hō-mō-jē′nē-ŭs). Of uniform structure or composition throughout. [homo- + G. *genos,* race]

ho·mo·gen·e·sis (hō-mō-jen′ĕ-sis). Production of offspring similar to the parents, in contrast to heterogenesis. SYN homogeny. [homo- + G. *genesis,* production]

ho·mog·e·ni·za·tion (hŏ-moj′ĕ-ni-zā′shŭn). The process by which a material is made homogeneous.

ho·mog·e·nize (hŏ-moj′ĕ-nīz). To make homogeneous.

ho·mog·e·nous (hō-moj′ĕ-nŭs). Having a structural similarity because of descent from a common ancestor. Commonly confused with homogeneous. [homo- + G. *genos,* family, kind]

ho·mo·gen·tis·ate 1,2-di·ox·y·gen·ase (hō-mō-jen′tis-āt). An iron-containing enzyme that catalyzes the oxidative cleavage of the benzene ring in homogentisic acid by O_2, forming 4-maleylacetoacetate; an absence or deficiency of this enzyme will result in alcaptonuria. SYN homogentisic acid oxidase.

ho·mo·gen·tis·ic ac·id (hō′mō-jen-tis′ik). Glycosuric acid; (2,5-dihydroxyphenyl)acetic acid; an intermediate in L-phenylalanine and L-tyrosine catabolism; if made alkaline, it oxidizes rapidly in air to a quinone that polymerizes to a melanin-like material; elevated levels are observed in individuals having alcaptonuria. SYN alcapton, alkapton.

h. a. oxidase, SYN homogentisate 1,2-dioxygenase.

ho·mog·e·ny (hō-moj′ĕ-ne). SYN homogenesis.

ho·mo·gly·can (hō-mō-glī′kan). A polysaccharide consisting of only one type of monosaccharide subunit (*e.g.,* glucan). Cf. heteroglycan, glycan.

ho·mo·graft (hō′mō-graft). SYN allograft *rejection.*

ho·moi·o·pla·sia (hō′moy-ō-plā′zē-ă). SYN homeoplasia.

ho·moi·o·ther·mal (hō-moy-ō-ther′măl). SYN homeothermic.

ho·mo·kar·y·on (hō-mō-kar′ē-on). Genetically identical multiple nuclei in a common cytoplasm, usually resulting from fusion of two cells from the same species. [homo- + G. *karyon,* kernel, nut]

ho·mo·kar·y·ot·ic (hō-mō-kar-ē-ot′ik). Exhibiting the properties of a homokaryon.

ho·mo·ker·a·to·plas·ty (hō′mō-ker′ă-tō-plas-tē). Corneal transplant between members of the same species.

ho·mo·lat·er·al (hō-mō-lat′er-ăl). SYN ipsilateral. [homo- + L. *latus,* side]

ho·mo·lip·ids (hō-mō-lip′idz). Lipids containing only C, H, and O. Cf. heterolipids. SYN simple lipids.

ho·mo·log, ho·mo·logue (hom′ō-log). A member of a homologous pair or series. [homo- + G. *logos,* word, ratio, relation]

ho·mol·o·gous (hŏ-mol′ō-gŭs). Corresponding or alike in certain critical attributes. **1.** In biology or zoology, denoting organs or parts corresponding in evolutionary origin and similar to some extent in structure, but not necessarily similar in function. **2.** In chemistry, denoting a single chemical series, differing by fixed increments. **3.** In genetics, denoting chromosomes or chromosome parts identical with respect to their construction and genetic content. **4.** In immunology, denoting serum or tissue derived from members of a single species, or an antibody with respect to the antigen that produced it. [see homologue]

ho·mol·o·gy (hŏ-mol′ō-jē). The state of being homologous.

h. of chains, the degree of similarity between the base sequences of strands of two DNAs. SYN h. of strands.

DNA h., the degree (or percentage) of hybridization capable between the DNA of different microorganisms.

h. of strands, SYN h. of chains.

ho·mol·y·sin (hŏ-mol′i-sin). A sensitizing hemolytic antibody (hemolysin) formed as the result of stimulation by an antigen derived from an animal of the same species. [homo- + hemolysin]

ho·mol·y·sis (hō-mol′i-sis). Lysis of red blood cells by a homolysin and complement.

ho·mo·mor·phic (hō-mō-mōr′fik). Denoting two or more structures of similar size and shape. [homo- + G. *morphē,* shape, appearance]

ho·mon·o·mous (hō-mon′ō-mŭs). Denoting parts, having similar form and structure, arranged in a series, as the fingers or toes. [G. *homonemos,* under the same laws, fr. *homos,* same, + *nomos,* law]

ho·mon·o·my (hō-mon′ō-mē). The condition of being homonomous.

ho·mo·nu·cle·ar (hō-mō-nū′klē-er). Denoting a cell line that retains the original chromosome complement.

ho·mon·y·mous (hō-mon′i-mŭs). Having the same name or expressed in the same terms, *e.g.,* the corresponding halves (right or left, superior or inferior) of the retinas. [G. *homōnymous,* of the same name, fr. *onyma,* name]

ho·mo·phenes (hō′mō-fēnz). Words in which the visible organs of speech behave the same, *e.g.,* tug, tongue, tuck.

ho·mo·phil (hō′mō-fil). Denoting an antibody that reacts only with the specific antigen which induced its formation. [homo- + G. *philos,* fond]

ho·mo·plas·tic (hō-mō-plas′tik). Similar in form and structure, but not in origin. [homo- + G. *plastos,* formed]

ho·mo·plas·ty (hō′mō-plas′tē). Repair of a defect by a homograft.

ho·mo·pol·y·mer (hō-mō-pol′i-mer). A polymer composed of a series of identical radicals; *e.g.,* polylysine, poly(adenylic acid), polyglucose.

ho·mo·pro·line (hō-mō-prō′lēn). SYN pipecolic acid.

ho·mo·pro·to·cat·e·chu·ic ac·id (hō′mō-prō′tō-kat-ĕ-chū′ik). (3,4-Dihydroxyphenyl)acetic acid; an isomer of homogentisic acid found in urine; a degradation product of L-tyrosine, L-dopa, and hydroxytyramine.

hom·or·gan·ic (hom-ōr-gan′ik). Produced by the same organs, or by homologous organs.

ho·mo·sal·ate (hō-mō-sal′āt). 3,3,5-Trimethylcyclohexyl salicylate; an ultraviolet screening agent for topical application to the skin.

ho·mo·sced·as·tic·i·ty (hō′mō-skĕ-das-tis′ĭ-tē). Constancy of the variance of a measure over the levels of the factor under study.

ho·mo·ser·ine (hō-mō-ser′ēn). $HOCH_2CH_2CH(NH_2^+)COO^-$; 2-amino-4-hydroxybutyric acid; a hydroxyamino acid differing from serine in the possession of an additional CH_2 group; formed in the conversion of L-methionine to L-cysteine.

h. deaminase, SYN cystathionine γ-lyase.

h. dehydratase, SYN cystathionine γ-lyase.

h. lactone, the cyclic ester (*i.e.,* the δ-lactone) of h.; formed by the reaction of cyanogen bromide on methionyl residues in peptides and proteins.

ho·mo·sex·u·al (hō-mō-sek′shū-ăl). **1.** Relating to or characteristic of homosexuality. **2.** One whose interests and behavior are characteristic of homosexuality. SEE Gay, lesbian.

ho·mo·sex·u·al·i·ty (hō′mō-sek-shū-al′i-tē). Erotic attraction, predisposition, or activity, including sexual congress, between individuals of the same sex, especially past puberty. SYN homoerotism, homoeroticism.

ego-dystonic h., a psychological or psychiatric disorder in which

ho

...o·sis (an-ār-ō-bī-ō'sis). Existence in an oxygen-free atmosphere. [G. *an-* priv. + *aēr*, air, + *biōsis*, way of living]

an·aer·o·gen·ic (an-ār-ō-jen'ik). Not producing gas. [G. *an-* priv. + *aēr*, air, + *-gen*, producing]

an·aer·o·phyte (an-ār'ō-fīt). **1.** A plant that grows without air. **2.** An anaerobic bacterium. [G. *an-* priv. + *aēr*, air, + *phyton*, plant]

an·aer·o·plas·ty (an-ār'ō-plas-tē). Treatment of wounds by exclusion of air. [G. *an-* not + *aēr*, air, + *plastos*, formed]

an·a·gen (an'ă-jen). Growth phase of the hair cycle, lasting about 3 to 6 years in human scalp hair. [G. *ana*, up, + *-gen*, producing]

an·a·gen·e·sis (an-ă-jen'ĕ-sis). **1.** Repair of tissue. **2.** Regeneration of lost parts. [G. *ana*, up, + *genesis*, production]

an·a·ge·net·ic (an'ă-jĕ-net'ik). Pertaining to anagenesis.

an·a·ges·tone ac·e·tate (an-ă-jes'tōn). 17-Hydroxy-6α-methylpregn-4-en-20-one acetate; a progestational agent.

Anagnostakis, Andrei, Cretan ophthalmologist, 1826–1897.

an·a·go·gy (an-ă-gō'jē). Psychic content of an idealistic or spiritual nature. [G. *anagōgē*, fr. *an- ago*, to lead up]

an·a·kat·a·did·y·mus, an·a·cat·a·did·y·mus (an'ă-kat-ă-did'i-mŭs). Conjoined twins united in the middle but separated above and below. SYN diecephalus dipygus. [G. *ana*, up, + *kata*, down, + *didymos*, twin]

an·á·khré (an-ah-krā'). SYN goundou. [Fr. fr. Af. native term meaning "big nose"]

an·ak·me·sis (an-ak'mē-sis). Arrest of maturation of leukocytes in their production centers, thereby resulting in greater numbers of young forms and progressively smaller proportions of mature granular cells in the bone marrow, as observed in agranulocytosis. [G. *an-* priv. + *akmēnos*, full grown, fr. *akmē*, highest point]

an·a·ku·sis (an-ă-kū'sis). SYN anacusis.

anal (ā'năl). Relating to the anus.

an·al·bu·mi·ne·mia (an'al-bū-mi-nē'mē-ă). Absence of albumin from the serum. [G. *an-* priv. + albumin + G. *haima*, blood]

an·a·lep·tic (an-ă-lep'tik). **1.** Strengthening, stimulating, or invigorating. **2.** A restorative remedy. **3.** A central nervous system stimulant, particularly used to denote agents that reverse depressed central nervous system function. [G. *analēptikos*, restorative]

an·al·ge·sia (an-ăl-jē'zē-ă). A neurologic or pharmacologic state in which painful stimuli are so moderated that, though still perceived, they are no longer painful. Cf. anesthesia. [G. insensibility, fr. *an-* priv. + *algēsis*, sensation of pain]

a. al'gera, SYN a. dolorosa.

conduction a., SYN regional *anesthesia*.

a. doloro'sa, spontaneous pain in a body area that lacks sensation. SYN a. algera.

inhalation a., a. produced by inhalation of a central nervous system depressant gas (especially nitrous oxide) or vapor.

patient controlled a. (PCA), a method for control of pain based upon a pump for the constant intravenous or, less frequently, epidural infusion of a dilute narcotic solution that includes a mechanism for the self-administration at predetermined intervals of a predetermined amount of the narcotic solution should the infusion fail to relieve pain. SYN outpatient anesthesia (1).

spinal a., euphemism for spinal *anesthesia*.

an·al·ge·sic (an-ăl-jē'zik). **1.** A compound capable of producing analgesia, *i.e.*, one that relieves pain by altering perception of nociceptive stimuli without producing anesthesia or loss of consciousness. SYN analgetic (1). **2.** Characterized by reduced response to painful stimuli. SYN antalgic.

an·al·ge·sim·e·ter (an'ăl-jē-zim'i-ter). A device for eliciting painful stimuli in order to measure pain under experimental conditions. [analgesia + G. *metron*, measure]

an·al·get·ic (an-ăl-jet'ik). **1.** SYN analgesic (1). **2.** Associated with decreased pain perception.

anal·i·ty (ā-nal'i-tē). Referring to the psychic organization derived from, and characteristic of, the Freudian anal period of psychosexual development.

an·al·ler·gic (an-ă-ler'jik). Not allergic.

an·a·log (an'ă-log). **1.** One of two organs or parts in different species of animals or plants which differ in structure or development but are similar in function. **2.** A compound that resembles another in structure but is not necessarily an isomer (*e.g.*, 5-fluorouracil is an analog of thymine); a.'s are often used to block enzymatic reactions by combining with enzymes (*e.g.*, isopropyl thiogalactoside vs. lactose). SYN analogue. [G. *analogos*, proportionate]

enzyme a., SYN synzyme.

anal·ogous (ă-nal'ō-gŭs). Possessing a functional resemblance, but having a different origin or structure.

an·a·logue (an'ă-log). SYN analog.

an·al·pha·lip·o·pro·tein·e·mia (an-al'fă-lip'ō-prō'tēn-ē'mē-ă) [MIM*205400]. Familial high density lipoprotein deficiency; a heritable disorder of lipid metabolism characterized by almost complete absence from plasma of high density lipoproteins, and by storage of cholesterol esters in foam cells, tonsillar enlargement, an orange or yellow-gray color of the pharyngeal and rectal mucosa, hepatosplenomegaly, lymph node enlargement, corneal opacity, and peripheral neuropathy; autosomal recessive inheritance. SYN familial high density lipoprotein deficiency, Tangier disease. [G. *an-*, priv., + *alpha*, α, + lipoprotein + *-emia*, blood]

anal·y·sand (ă-nal'i-sand). In psychoanalysis, the person being analyzed. [analysis + L. *-andus*, gerundive ending]

anal·y·sis, pl. **anal·y·ses** (ă-nal'i-sis, -sēz). **1.** The breaking up of a chemical compound or mixture into simpler elements; a process by which the composition of a substance is determined. **2.** The examination and study of a whole in terms of the parts composing it. **3.** SEE psychoanalysis. [G. a breaking up, fr. *ana*, up, + *lysis*, a loosening]

accumulation a., a technique in which an intermediate of a metabolic pathway accumulates due to selective inhibition of a particular step in that pathway or in a mutant that is deficient in a certain step. The intermediate is then isolated, analyzed, and identified.

activation a., the identification and quantification of unknown elements from their characteristic emissions and decay constants after they have been made radioactive by exposure to neutron or charged particle radiation.

amino acid a., **(1)** determination and identification of amino acid content of a macromolecule; **(2)** identification of a specific amino acid in macromolecules, often a mutated protein; **(3)** identification and quantitation of amino acid content in blood plasma or urine; a key diagnostic aid.

bite a., SYN occlusal a.

blood gas a., the direct electrode measurement of the partial pressure of oxygen and carbon dioxide in the blood.

bradykinetic a., the a. of a movement by means of slow cinematography.

cephalometric a., a study of the skeletal and dental relationships used in orthodontic case a.

character a., a. of the defenses and personality traits that characterize an individual.

cluster a., a set of statistical methods used to group variables or observations into strongly interrelated subgroups.

content a., any of a variety of techniques for classification and study of the verbal products of normal or of psychologically disabled individuals.

decision a., a derivative of operations research and game theory that involves identifying all available choices and the potential outcomes of each, in a series of decisions that have to be made about patient care—diagnostic procedures, therapeutic regimens, prognostic expectations; the range of choices can be plotted on a decision tree.

didactic a., SYN training a.

discriminant a., a statistical analytic technique used with discrete dependent variables, concerned with separating sets of observed values and allocating new values; an alternative to regression analysis.

displacement a., SYN competitive binding *assay*.

distributive a., the a. of information gained about the patient and its distribution by the physician, as indicated by the patient's complaint and symptoms.